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VIEWPOINT

Heart Failure Therapy at a Crossroad: Are There Limits to the Neurohormonal Model?

Mandeep R. Mehra, MD, FACC,* Patricia A. Uber, PHARMD,* Gary S. Francis, MD, FACC†
New Orleans, Louisiana; and Cleveland, Ohio

The advent of neurohormonal blockade in heart failure (HF) has been an overwhelming success, but current evidence points to a ceiling effect as newer neurohormonal targets are exploited in an incremental manner. This has lead us to question whether the neurohormonal model of HF can be sustained by simply stacking multiple neurohormonal or cytokine blockers together as treatment. A unifying theme in some of these disparate trials relates to either a lack of efficacy or, more importantly, adversity resulting in regression of already achieved benefits. It is our contention that the available evidence has uncovered the remarkable complexity of interaction within the context of the neurohormonal construct. As we stand at a crossroad in HF and begin to fervently pursue non-neurohormonal therapeutic targets, we must also direct attention at navigating the multifaceted labyrinth of the neurohormonal model that has led to the current imbroglio. (J Am Coll Cardiol 2003;41: 1606–10) © 2003 by the American College of Cardiology Foundation

Neurohormonal mechanisms that counteract adverse homeostatic imbalance such as salt and water loss evolved as an important survival trait. Thus, our primal instincts to gather food by wildlife hunting and survive on dry land without ready access to salt and water were supported by the creation of defense systems to ward off deleterious effects emanating from volume loss. In this regard, the human physiology was entrained to respond rapidly to an acute or chronic perturbation of the cardiovascular system by implementing salt and water retention, vasoconstriction, increased heart rate, and hemostatic mechanisms focused on thrombosis and eventually tissue repair (1). Heart failure (HF) is a clinical syndrome characterized by chronic, persistent activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (2). In HF, the homeostatic mechanisms seem activated in response to a perceived reduction in circulating blood volume. The resultant effect is the development of a vicious cycle characterized by excessive neurohormonal stimulation that is responsible not only for the chronic expression of adverse hemodynamic abnormalities but also myocardial and vascular remodeling, a hallmark of progressive HF.

Our recognition of this very tenet has led us to shift therapy in HF from drugs designed to enhance positive inotropic status to those designed to halt the progression of disease (remodeling). It is the latter that favorably influences survival? The evolution of the era of angiotensin-converting enzyme (ACE) inhibitors followed by the application of anti-adrenergic therapies has been more successful than originally envisioned (3). The success accrued from inhibiting two persistently active neurohormonal systems has led to the proposition that a concerted systematic approach to inhibit every single errant neurohormonal or cytokine pathway may continue to provide incremental benefits. However, recent clinical trial data evaluating this all-encompassing strategy have yielded startlingly disappointing results leading us to question whether the neurohormonal model of HF can be sustained by simply stacking multiple neurohormonal or cytokine blockers together as treatment.

MORE IS NOT NECESSARILY BETTER

Our suggestion of a neurohormonal threshold of benefit in HF beyond which "more complete blockade" (as with higher-dose ACE inhibitors or complimentary angiotensin receptor antagonism), adjunctive endothelin antagonist use, cytokine (tumor necrosis factor [TNF]-alpha) blockade, or, more recently, by the conjoint application of the vasopeptidase inhibitor omapatrilat stems from the failure of these strategies to add incremental value. A unifying theme in some of these disparate trials relates to either a lack of efficacy or, more importantly, adversity resulting in regression of already achieved benefits (Fig. 1).

Is higher-dose ACE inhibition beneficial? The first inclination to the phenomenon of a neurohormonal ceiling emerged with the rather surprising findings from the Assessment of Treatment with Lisinopril And Survival (ATLAS) trial wherein only modest benefits on morbidity, but not mortality, were noted when low-dose ACE inhibitors (lisinopril, 2.5 to 5 mg daily) were compared with high-dose ACE inhibitors (lisinopril, 35 mg daily) (4). In this trial, 3,164 patients with New York Heart Association (NYHA) functional class II to IV HF and an ejection fraction ≤30% were randomized to double-blind treatment with either low

From the *Department of Cardiovascular Medicine, Ochsner Clinic Foundation, New Orleans, Louisiana; and the †Department of Cardiology, Cleveland Clinic Foundation, Cleveland, Ohio. Drs. Mehra and Francis have both served as consultants or received honoraria from Bristol Myers Squibb, Merck, Astra Zeneca, and Glaxo Smith Kline.

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ARB = angiotensin receptor antagonists
HF = heart failure
NEP = neutral endopeptidase
NYHA = New York Heart Association
RAAS = renin-angiotensin-aldosterone system
TNF = tumor necrosis factor

doses (2.5 to 5.0 mg daily, n = 1,596) or high doses (32.5 to 35 mg daily, n = 1568) of the ACE inhibitor lisinopril for 39 to 58 months, while background therapy for HF was continued. When compared with the low-dose group, patients in the high-dose group had a nonsignificant 8% lower risk of death ($p = 0.128$) but a significant 12% lower risk of death or hospitalization for any reason ($p = 0.002$) and 24% fewer hospitalizations for HF ($p = 0.002$). Dizziness and renal insufficiency was observed more frequently in the high-dose group, but the two groups were similar in the number of patients requiring discontinuation of the study medication. Although these data were accrued before the widespread application of anti-adrenergic therapy, it was viewed with satisfaction that perhaps even low-dose ACE inhibitors might successfully provide some degree of benefit and that more robust clinical outcomes would not necessarily be achieved by pushing ACE inhibitors to high doses. A recent study by Nanas et al. (5) that investigated the use of very high-dose ACE inhibitors (enalapril, 60 mg daily) compared with standard therapeutic doses failed to demonstrate significant benefit. In this trial, no survival benefits were noted in the high-dose ACE inhibitor group, and the tolerability of this regimen was limited as evidenced by an excessive withdrawal rate and poorer compliance. More recently, Tang et al. (6) conducted a small trial to investigate whether high-dose enalapril (40 mg daily) was better on neurohormonal end points than low doses of this drug (5 mg daily). Surprisingly, the low-dose group performed equally well compared with the high-dose group in suppression of the sentinel neurohormonal parameters including angiotensin II, aldosterone, and catecholamines.

Is dual RAAS inhibition better? The addition of angiotensin receptor antagonists (ARB) to a stable regimen of ACE inhibitors and beta-antagonists has also suggested that this approach may not be warranted. In the Valsartan in Heart Failure Trial (Val-HeFT), results after a mean follow-up of 1.89 years indicated that the addition of valsartan did not affect overall mortality but reduced rehospitalizations for HF (7). Subgroup analyses revealed that the majority of this benefit was accrued from the group of patients not taking ACE inhibitors. However, among one-third of patients receiving triple therapy (ACE inhibitors, ARBs, and beta-blocker), all-cause morbidity and mortality demonstrated an unfavorable harmful trend. This important observation requires verification. Additional data may emerge from the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial where more than one-half of all

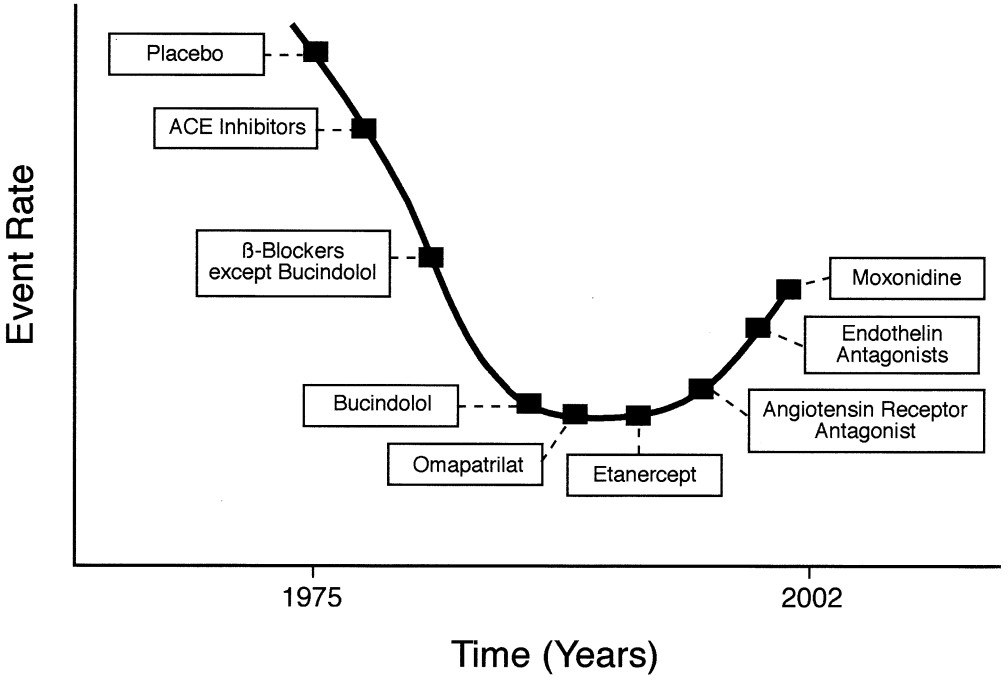

Figure 1. Saturation of benefits with incremental neurohormonal blockade in chronic heart failure (1975–2003). The **curve** represents directional tendency rather than exact point estimates of benefit or adverse outcomes. Spironolactone is not included because the supporting data are from a single large trial constructed in a distinct population of unstable and severe heart failure patients with low background use of beta-blockers. ACE = angiotensin-converting enzyme.

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15,000 patients enrolled are receiving so-called "triple therapy."

Are neutral endopeptidase (NEP) and endothelin antagonists useful? Omapatrilat, a vasopeptidase inhibitor, represents a new class of agents designed to inhibit both the ACE and NEP, and not only reduces the production of angiotensin II but also inhibits degradation of bradykinin, natriuretic, and many other peptides (8); NEP inhibitors may also increase plasma concentrations of endothelin, a potentially adverse effect because endothelin is a substrate for NEP (9). More recently, the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) HF trial results were reported in 5,770 patients with symptomatic (NYHA functional class II to IV) systolic HF (left ventricular ejection fraction <0.30) and a HF hospitalization within the last 12 months (10). They were all receiving optimal therapies, and 50% were on beta-blockers, 40% on spironolactone, and 60% on digoxin. They were then randomized to enalapril (10 mg twice a day) or omapatrilat (40 mg once daily). The primary end point (combined risk of death or hospitalization for HF requiring intravenous treatment) was used prospectively to test both a superiority and noninferiority hypothesis. The primary end point fulfilled prespecified criteria for noninferiority but not for superiority (973 patients in the enalapril group, and 914 patients in the omapatrilat group; hazard ratio, 0.94; $p = 0.187$). The omapatrilat group also had a 9% lower risk of cardiovascular death or hospitalization ($p = 0.024$) and a 6% lower risk of death ($p = 0.339$). Adverse effects showed a higher rate of hypotension and dizziness with omapatrilat. Angioedema, which has been an issue with omapatrilat in the treatment of hypertension, was only slightly increased in the omapatrilat group in this study. The lack of incremental benefit with omapatrilat may have been due to a resistance to endogenous natriuretic peptides or to an increase in hypotension episodes that may have neutralized benefits in those patients with HF and higher baseline blood pressures. Additionally, the dose of omapatrilat used may have been incorrect. Nevertheless, it is troubling that enhancement of counter-regulatory peptides failed to add benefit (10).

Equally discouraging findings from trials using endothelin antagonists are forthcoming. Two agents, enrasanten and bosentan, have both failed to demonstrate a significant benefit in optimally treated systolic HF (11,12). In particular, the Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure (ENABLE) trial evaluated more than 1,600 patients with severe systolic HF to determine the effect of this agent on all-cause mortality and HF hospitalizations. No benefits were observed with this agent, but the bosentan-treated group had weight gain.

Is excess sympatholysis beneficial or adverse? Inhibition of the sympathetic nervous system by a centrally acting sympatholytic agent, moxonidine, was studied in the Moxonidine in Congestive Heart Failure (MOXCON) trial in patients with symptomatic HF (13). The study was terminated early because of higher mortality in the moxonidine group. A subinvestigation further demonstrated marked lowering of norepinephrine levels (13). This finding has led to the suggestion that perhaps the dose of moxonidine might have been too high, or the titration rate of moxonidine was too rapid. Rebound sympathetic activation between doses may also have occurred, contributing to increased fatality. In the Beta-blocker Evaluation of Survival Trial (BEST) study, bucindolol similarly led to a profound sympatholysis that was associated with excess mortality (14). Compared with placebo, bucindolol lowered norepinephrine by 19% at three months. A surprising nonlinear relationship effect on prediction of outcome as a function of plasma norepinephrine levels was observed. Thus, a higher mortality was noted in those groups that demonstrated either an increase of norepinephrine over time or a marked decrease (>-758 pg/ml). Data such as these point to the fact that excess sympatholysis may be harmful in the syndrome of HF.

Is cytokine antagonism useful? In a preliminary investigation of etanercept, a drug that functionally inactivates TNF-alpha binding sites, improvement in ventricular remodeling was noted (15). After three months, a reduction in left ventricular end-diastolic volumes with small enhancements in ejection fraction were seen, along with improvements in quality of life and clinical scores of HF severity. These preliminary findings were then used to support conduction of a large survival study, the Randomized Etanercept North AmerIcan Strategy to Study ANtagonism of CytokinEs (RENNAISSANCE) and Research into Etanercept Cytokine Antagonism and Ventricular Dysfunction trial (RECOVER). Unfortunately, the RENNAISSANCE trial was stopped prematurely due to a determination that this trial would not be able to demonstrate efficacy of this cytokine antagonism approach, and that this strategy may even be harmful (10). More recently, the combined results of RECOVER and RENNAISANCE under the umbrella of the Randomised EtaNErcept Worldwide evALuation (RENEWAL) trial were presented. The RENEWAL trial combined data on the patients randomized to placebo or 25 mg of etanercept twice a week from RECOVER and the patients randomized to placebo, 25 mg of etanercept twice a week, or 25 mg of etanercept three times per week from RENAISSANCE. The primary end point for RENEWAL was the combined morbidity/mortality end point of death or congestive HF hospitalization, and the secondary end point was all-cause mortality. A trend was seen toward worsening outcomes for the primary end point in the RENAISSANCE trial ($p = 0.17$), in which patients were followed for a mean of 12.7 months after randomization. There was no change from baseline in patients on treatment, followed for a mean of 5.7 months in the RECOVER trial. Another TNF-alpha antagonist, infliximab, has also failed to show a benefit in patients with CHF (16).

Aldosterone antagonists: a glimmer of hope? Spironolactone in nondiuretic doses appears to provide incremental

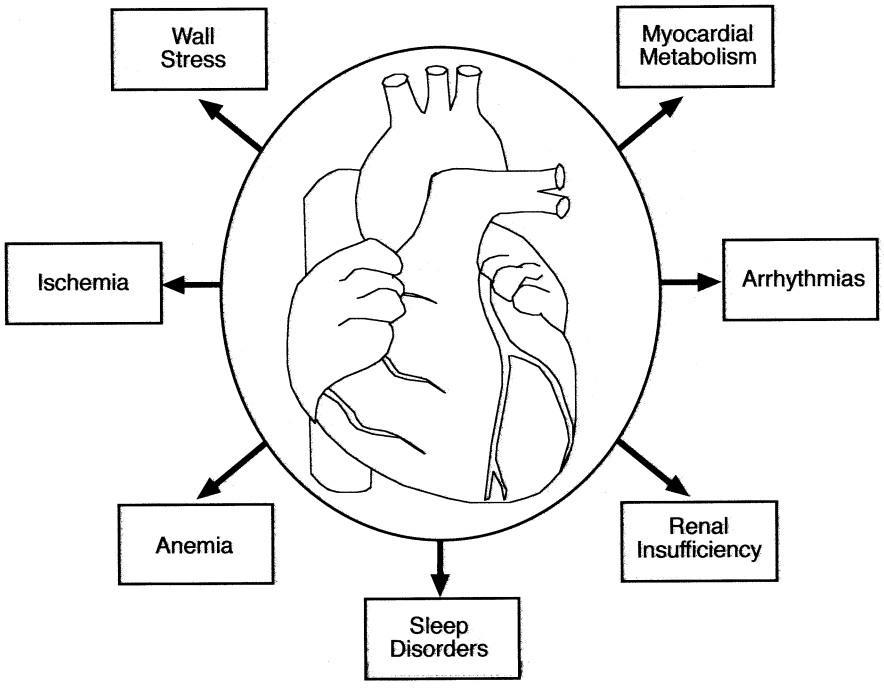

Figure 2. Potential therapeutic targets beyond the neurohormonal model. Emerging investigations are focusing on amelioration of wall stress by using surgical remodeling and resynchronization therapy. Other important strategies are tackling myocardial metabolism, ischemia abrogation, sudden death prevention, anemia, sleep disorders, and renal insufficiency in heart failure.

benefits to ACE inhibitors. Pitt et al. (17) reported a convincing benefit on survival, HF hospitalizations, and symptoms with low-dose spironolactone in severe HF. It should be noted that this trial was conducted exclusively in patients with severe HF, few patients received beta-blockers, and blood pressure was not lowered with this small dose of spirolnolactone. It is quite possible that spironolactone exerts its sentinel effects by targeting cardiac structural abnormalities in the extracellular matrix. Zannad et al. (18) studied the effects of spironolactone on markers of cardiac fibrosis and suggested that high baseline serum levels of markers of cardiac fibrosis synthesis were significantly associated with poor outcome and were decreased during spironolactone therapy. The benefit from spironolactone was confined in patients with higher levels of collagen turnover. The results suggest that limitation of the excessive extracellular matrix turnover may be one of the various extra renal mechanisms contributing to the beneficial effect of spironolactone in patients with HF.

EMERGING THERAPEUTIC TARGETS

As the totality of current evidence suggests a limit to multiple neurohormonal blocking drugs to treat HF, it is important for us to derive other therapeutic strategies in an effort to incrementally influence morbidity and mortality in HF. These specific strategies include modulation of myocardial metabolic substrate utilization, alleviation of myocardial ischemia, and relief of arrhythmic burden. Other novel areas of investigation relate to identifying and treating sleep disordered breathing, amelioration of anemia and renal dysfunction, and resynchronization of contraction as well as use of other anti-remodeling devices (19–34) (Fig. 2).

CONCLUSIONS

In summary, the advent of neurohormonal blockade in HF has been an overwhelming success, but current evidence points to a ceiling effect. Pharmacotherapy designed to block the RAAS has served us well, and, save for a few notable non-successes, so have adrenergic inhibitors. Do the current data signal demise of the neurohormonal model with regard to stack-on blockade beyond RAAS and adrenergic targets? It is our contention that the available evidence has uncovered the remarkable complexity of interaction within the context of the neurohormonal construct. As we stand at a crossroad in HF and begin to fervently pursue non-neurohormonal therapeutic targets, we must also direct attention at navigating the multifaceted labyrinth of the neurohormonal model that has led to the current imbroglio.

Reprint requests and correspondence: Dr. Mandeep R. Mehra, Cardiomyopathy and Heart Transplantation Center, BH-326, 1514 Jefferson Highway, New Orleans, Louisiana 70121. E-mail: mmehra@ochsner.org.

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